

Elsea. The examiner states that Thomson teaches human embryonic stem cells from IVF embryos and teaches that genetic modifications could be produced in ES cells for reducing or combating immune rejection. The examiner states that Thomson further teaches the production of cell lines from the human ES cells and that human ES cells can be differentiated by allowing the cells to grow to confluence and that human ES cells would be valuable in studies of development and function of tissues that differ between mice and humans and that screens based upon the *in vitro* differentiation to specific lineages could identify gene targets for new drugs. The examiner concedes that Thomson does not teach that the embryos used would have a naturally occurring disease mutation. However, the examiner states that Harper teaches that human embryos can be screened for certain diseases by PCR. The examiner cites Jessell as teaching methods of identifying candidate agents for treating conditions associated with motor neuron degeneration by obtaining embryonic stem cells wherein the stem cells contain a mutation of a specific gene, contacting the ES cells with retinoic acid to differentiate the cells into neural progenitor cells, and determining the effect of an agent for use in treatment of a condition associated with motor neuron degeneration. The examiner states that one of skill in the art would have been able to

use the methods of screening human embryos for specific disease causing mutations and use those embryos in the methods taught by Thomson in order to produce isolated ES cell lines with a naturally occurring disease causing mutation with a reasonable expectation of success and that persons of skill in the art would have been motivated to make these types of ES cells in order to use them in *in vitro* assays for identification of targets for new drugs as suggested by Thomson or to analyze the molecular mechanisms of the disease by allowing the ES cells to differentiate. The examiner considers it obvious to utilize the resultant cells and methods of screening agents suitable for treating a disorder such as the methods taught by Jessell with a reasonable expectation of success. The examiner states that Elsea provides guidance to show the various mouse models of human diseases do not produce a biochemical model that reproduces clinical symptoms and therefore show a need in the art to produce cells that could be used for screening various human diseases using human cells. This rejection is respectfully traversed.

This rejection must fall because the disclosure of Jessell relied upon by the examiner does not have an effective date as a reference which is prior to the effective filing date of the present application.

Submitted herewith is a listing of the claims that were filed with the filing of the application that issued as the Jessell patent, as well as each listing of claims in every amendment filed during the course of prosecution of the Jessell application. It can be seen that the first time a claim was presented with a step of obtaining or generating a culture of human embryonic stem cells, "wherein said embryonic stem cells contain a mutation in a gene selected from the group consisting of a superoxide dismutase gene and a survival motor neuron protein gene, said mutation associated with motor neuron generation," was the very last amendment prior to allowance, filed on November 21, 2007. Also submitted herewith is the complete amendment as filed in the Jessell application on November 21, 2007. While the first paragraph of the remarks states that none of the amendments constitutes new matter, this document does not show where in the specification there is support for obtaining human embryonic stem cells with a disease causing mutation. Support for that language is not proffered anywhere else in that amendment.

A review of the Jessell specification will show that there is no disclosure therein of any means to obtain human ES cells bearing a disease causing mutation. The only disclosure of obtaining embryonic stem cells with disease causing mutations is through the use of non-human transgenic animals

(of course, there is no such thing as a human transgenic animal). The use of neuronal cells having mutations in the SOD or SMN genes is disclosed, for example, in the paragraph beginning at line 30 of column 19. The last two sentences of this paragraph read:

For such a comparison, both the healthy and the diseased neural cells may be produced using well-known techniques and methods described herein. Alternatively, cells carrying SOD or SMN mutations may be isolated from living or dead patients who have ALS or SMA.

The "well known techniques and methods described herein" all involve use of transgenic non-human animals. The reference to isolating SOD or SMN mutations from living or dead patients who have ALS or SMA is the only mention of a way to get such mutated human cells. It has nothing to do with obtaining human embryonic stem cells carrying SOD or SMA mutations. Thus, the art is taught that this is getting cells from living ALS or SMA patients is the only way to get such human cells. There is no suggestion that mutated human embryonic cells can be obtained or how to obtain them.

The paragraph beginning at line 14, of column 20, defines the term "transgenic non-human animal" and states that the term "transgene" refers to, *inter alia*, "modified or mutated form of the gene that is endogenous to the animal" (column 20, line 22). In the paragraph beginning at column

20, line 56, Jessell states that the transgenic animal may have a genome in which the SOD or SMN gene is mutated.

In the paragraph beginning at line 7 of column 24, Jessell again states that the degenerated neurons carrying a mutation in an SOD or SMN gene may be isolated from a transgenic animal of the present invention whose genome contains a mutated SOD or SMN gene.

Accordingly, claim 3 of the Jessell patent is not supported by the Jessell disclosure as originally filed and therefore is not entitled to an effective date under 35 USC 102(e) as of the filing date of the application. Instead, the earliest effective date for such a disclosure is the date of issue of the Jessell patent, i.e., June 24, 2008, or, if amendments were made public upon filing as early as November 21, 2007, then the earliest possible effective date for this disclosure is the date of the amendment presenting that claim on November 21, 2007. The present application is the national stage of an international application filed on November 15, 2004, well prior to any effective date of this disclosure.

It should be noted that the Jessell patent was previously published as 2004/0014210. This publication does not have the disclosure relied upon by the examiner and thus could not have been used in the present rejection. If the 2004/0014210 publication does not have any disclosure of

obtaining human embryonic stem cell lines having a disease causing mutation, it could have not have been used as a substitute for the Jessell patent in the rejection. The Jessell patent cannot bootstrap a disclosure appearing only in the issued patent to make it available as a reference as of its filing date for subject matter that was not present in the application as filed, or as published on January 22, 2004.

The examiner's attention is drawn to MPEP 2136.02, which states in section II that:

Subject matter not included in the patent or application publication itself can only be used when the subject matter becomes public.

As the portion of Jessell relied upon by the examiner is not available as a reference as of the effective filing date of the present application, the entire rejection must fall.

The remaining references will not support an obviousness rejection. All that Thomson and Harper allegedly teach is that techniques existed to find mutated human embryonic stem cells as of the date of the present invention. All that Elsea teaches is that mouse models do not work with certain human diseases. None of this information would suggest the present invention at the time the present invention was made and without hindsight knowledge of the present invention. The case of Ex parte Levengood, 28 USPQ2d

1300, 1301-1302 (Bd.Pat.App.&Int. 1993) is instructive, where it states:

In this case, however, the only suggestion for the examiner's combination of the isolated teachings of the applied references improperly stems from appellant's disclosure and not from the applied prior art. ... At best, the examiner's comments regarding obviousness amount to an assertion that one of ordinary skill in the relevant art would have been able to arrive at appellant's invention because he had the necessary skills to carry out the requisite process steps. This is an inappropriate standard for obviousness. ... That which is within the capabilities of one skilled in the art is not synonymous with obviousness. ... That one can *reconstruct* and/or explain the theoretical mechanism of an invention by means of logic and sound scientific reasoning does not afford the basis for an obviousness conclusion unless that logic and reasoning also supplies sufficient impetus to have led one of ordinary skill in the art to combine the teachings of the references to make the claimed invention.

...

In the case before us, the examiner has provided references having teachings which go a long way towards providing a scientific explanation for *what happened* when appellant performed the claimed combination of process steps. However, the references themselves fall far short of providing the "motivation" or "suggestion" to assemble their teachings into a viable process. A *prima facie* case of obviousness has not been made out.
[Emphasis original]

Neither Thomson nor Harper suggest any use for mutated human embryonic cells. Elsea states a problem but does not suggest any solution. Thomson and Harper do not suggest that

solution. Only applicant's specification suggests the solution. As in the *Levengood* case, one can reconstruct the present invention or explain the theoretical mechanism of the present invention by piecing together the isolated disclosures of the prior art. But this is far short of providing the motivation or suggestion to assemble their teachings into a viable process. A *prima facie* case of obviousness has not been made out.

For all of these reasons, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 82 to 84 and 96-98 have been rejected under 35 USC 103(a) as being unpatentable over Thomson in view of Harper, in view of Jessell and Elsea and further in view of U.S. patent publication 2005/0054092 to Xu et al. (hereinafter referred to as Xu). This rejection is respectfully traversed.

In view of the fact that Jessell is not available as a reference as of the effective filing date of the present application for the reasons discussed above, the present rejection must fall for the same reasons as discussed above with respect to the rejection of claims 52, 55, 58-60, 74, 75, 78-80, 85, 86, 88-94 and 99-101. Accordingly, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 57, 81, 87 and 95 have been rejected under 35 USC 103(a) as being unpatentable over Thomson in view of

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Harper, in further view of Jessell and Elsea and further in view of U.S. Patent 5,972,995 to Fischer et al., hereinafter referred to as Fischer. This rejection is respectfully traversed.

Because this rejection also relies on the Jessell reference, which is not available as reference for the reasons discussed above, the present rejection must fall for the same reasons as the other two rejections already discussed above. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

It is submitted that all of the claims now present in this case fully definite over the references of record and fully comply with 35 USC 112. Reconsideration and allowance are therefore respectfully urged.

Respectfully submitted,

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